## REMARKS

### I. EXPLANATION OF AMENDMENTS.

#### A. The new sequence listing corrects typographical errors only.

The sequences in the amended sequence listing filed herewith are identical to the sequences in the previous sequence listing correction. The new sequence listing corrects inadvertent errors in the descriptive headings of SEQ ID NOs: 2 and 10. (SEQ ID NO: 2 had a typographical error "Blk" in field <223> for "Btk". SEQ ID NO: 10 was labeled at the <213> field as Artificial Sequence, but in fact it should be labeled as "Bacillus thuringiensis.") The amendment does not introduce new matter.

#### B. The new claims find support in the application and should be examined with the elected subject matter.

New claim 112 is similar to the other claims and generic to Groups I and II in the Restriction Requirement, insofar as claim 112 specifies starting with a sequence derived from *Bacillus*, which can be a sequence comprising a coding sequence for an insecticidal protein, or an amino acid sequence of the insecticidal protein. The "making" step of claim 112 can be practiced irrespective of the type of sequence with which one starts.

New independent claims 113 and 117, like the other claims, are directed to a method of making a structural gene that encodes an insecticidal protein. Both claims begin with a "designing" step that finds support throughout the application as originally filed. (The term "designing" also appeared in the preamble of claim 39, now canceled.) Claim 113, like other pending claims (e.g., claim 47), involves making a structural gene that encodes the insecticidal protein, and that is characterized by a reduced number of ATTTA sequences or Table II polyadenylation signal sequences, compared to wild type *Bacillus* coding sequence(s). Claim 117, like other pending claims, involves making a structural gene that encodes the insecticical protein, and that is substantially devoid of ATTTA sequences or substantially devoid of Table II polyadenylation signal sequences. Although new claims 113 and 117 both are directed to a method of making a structural gene with reduced numbers of the "problem sequences," these claims do not specify starting with a nucleotide or an amino acid sequence *per se*, and, in this respect, are generic to the three Groups in the restriction requirement.

New independent claim 119, like the other claims, is directed to a method of making a structural gene that encodes an insecticidal protein. Claim 119, step (a), specifies starting with a coding sequence derived from *Bacillus*, and thus would presumably be classified as part of Group I in the restriction requirement imposed by the Examiner. Step (b) of claim 119 is substantially identical to the "making" step of claim 59.

## II. THE SUBJECT MATTER OF THE CLAIMS

The present invention relates to a method of making a structural gene that encodes an insecticidal protein derived from *Bacillus* bacteria. At the time of the invention, it was appreciated that *Bacillus* bacteria produced insecticidal proteins, and *nucleotide sequences and deduced amino acid sequences* of such proteins had been published. However, efforts to express such proteins in plants had been disappointing. A need existed for improved expression.

The inventors determined the nature of a problem that existed with the *Bacillus* coding sequences in plants, and devised a solution. More specifically, the inventors determined that making a new coding sequence with fewer occurrences of certain "problem sequences" (ATTTA or polyadenylation signal sequences) than are found in wildtype *Bacillus* sequences results in improved expression (e.g., compared to a wild type sequence) when the new coding sequence is expressed in plants.

At least two closely related approaches are described in the patent application for "getting rid of" the problem sequences. In one approach, one starts with a *Bacillus* coding sequence (Group I claims), and identifies and removes one or more or the problem sequences, e.g., by substituting one or more codons in the region of the problem sequence. In a second approach, one starts with the amino acid sequence (Group II claims), and prepares a coding sequence, mindful of the detrimental effects of problem sequences, and avoiding them. With either approach, knowledge of the genetic code permits the making of a structural gene that still encodes an insecticidal protein amino acid sequence, even though – compared to wildtype *Bacillus* coding sequences – the number of problem sequences in the coding sequence has been reduced. With either approach, consideration is given to the coding sequence that is made (to avoid problem sequences) and consideration is given to the encoded amino acid sequence (to be insecticidal).

The inventors also teach that *Bacillus* insecticidal proteins have structurally conserved regions and regions that are non-essential for insecticidal activity, factors which permit recombination of sequences from different *Bacillus* genes to form chimeric genes that encode new insecticidal proteins. However, the native coding sequences still contain the problem sequences, when recombined. The inventors' solution to the problem of expression in plants – getting rid of the problem sequences – also is a solution for the recombined or chimeric genes.

## III. ELECTION

In response to the preliminary amendment and election filed by the Applicants on October 18, 2006, the Patent Office has issued another restriction requirement, alleging that the claims are directed to three distinct inventions.

All three allegedly distinct inventions are directed to methods of making a structural gene encoding an insecticidal protein. The Applicants understand the intended difference between the three restriction groups to be as follows:

Group I is defined by starting with a coding sequence;

Group II is defined by starting with an amino acid sequence; and

Group III is defined by recombining portions of two or more *Bacillus* sequences.

The Applicants elect Group I, claims 47-58, 69, 71-79, 81-83, 88-91, 93-94, 97-104, 106-107, and 110-111,with traverse.

Claims 108-109 depend from elected claims, and should also have been designated as corresponding, all or in part, to Group I.

As explained above in Section I of the remarks, new claims 112-119 should be examined along with the claims of Group I, even if the restriction requirement is maintained, because they are generic with respect to the starting material, or classifiable as part of Group I.

## IV. REJOINDER THROUGH RULE 129 AND PAYMENT OF ASSOCIATED FEES UNDER RULE 129.

As noted in the Applicants' response to the first restriction requirement, the present application is a "pre-GATT" application with an effective filing date more than three years prior to June 8, 1995. Thus, any restriction requirement evaluation, now or in the future, is subject to the provisions of 37 CFR 1.129, which modify "normal" restriction practice. The current restriction requirement makes no mention of Rule 1.129.

For reasons stated below, the Applicants believe that the restriction is without merit, and should be withdrawn in any case. However, the Applicants hereby authorize the Patent Office to charge the deposit account identified below up to twice the fee set forth in Rule 1.17(s) (currently $790) to expedite rejoinder of the two non-elected groups and examination of all of the claims on the merits. The authorization to charge the fees is solely to expedite examination on the merits by rendering moot the restriction requirement, and is not intended to be an acquiescence to the merits of the restriction or a waiver of any right to petition therefrom.

## V. TRAVERSAL OF RESTRICTION REQUIREMENT

### A. The interference history demonstrates that the restriction requirement is unnecessary and improper.

Prosecution of this application, filed in 1995, has resumed following resolution of a three application/patent interference. The interfering subject matter was defined in part by method claims that were pending in three involved applications/patents: the present application of Monsanto (Fischhoff); U.S. Patent No. 5,380,831 (Adang) of losing party Mycogen; and a second application now owned by Monsanto (Barton[1]). (See definition of "new Count 2" at p. 194 of of the Interference Opinion dated January 29, 2004, Paper No. 13, of record in the IFW for this application.) A review of the starting steps of the method claims involved in the interference demonstrates that the basis for the current restriction is improper, because the

[1] Junior party Barton's involved application was USSN 07/827,906, filed January 30, 1992. Monsanto was required to select one of its applications for the purposes of the interference, and selected the present Fischhoff application over the Barton application.

interference involved method claims that spanned all three Groups into which the Examiner now proposes to divide the current claims.

**1. The interference included Group I subject matter.**

Fischhoff's involved claim 3 (now canceled) was directed to a method of modifying a wild-type structural gene sequence and involved steps of removing problem sequences from the wild-type gene. The Examiner would presumably classify Fischhoff claim 3 within Group I of the current restriction requirement.

**2. The interference included Group II subject matter.**

In Barton's involved claim 1 (reproduced in below),[2] step (b) specifies synthesizing a chimeric nucleotide coding for the expression of the amino acid sequence of *B.t.* delta-endotoxin. As the claim concerns itself with synthesizing a chimeric coding sequence that encodes a target *amino acid sequence*, the Examiner would presumably classify Barton claim 1 with Group II of the current restriction requirement (starting with an amino acid sequence). (Step (b) of Barton is the relevant step for analysis for a "starting" *B.t.* sequence because it is the

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[2] Barton claim 1 reads as follows:

> 1. A method of improving the expression in a dicot plant of a Bacillus thuringiensis delta-endotoxin protein natively in excess of 72 kD in size and toxic upon ingestion to Manduca sexta, the method comprising the steps of:
>
> (a) analyzing the pattern of nucleotide codon usage in native plant genes having relatively high levels of expression in plants to select from among the codons coding for the same amino acid the codons for each amino acid which are utilized preferentially by the native plant genes;
>
> (b) synthesizing a chimeric nucleotide coding sequence coding for the expression of the amino acid sequence of the delta-endotoxin from Bacillus thuringiensis with the chimeric coding sequence comprising codons differing from those in the coding sequence in Bacillus thuringiensis and selected from among the codons determined from Figure 1 to be preferentially utilized by the native plant genes;
>
> (c) joining the chimeric nucleotide coding sequence with flanking regulatory sequences effective to express the chimeric coding sequence in plants; and
>
> (d) transforming the chimeric coding sequence together with the regulatory sequences into the germ line of the dicot plant so that the delta-endotoxin protein is produced in cells of the transformed plant so that the plant is toxic upon ingestion to Manduca sexta.

first step of the claim that pertains to the *B.t.* sequence. Step (a) pertains to analysis of codon usage in plant genes.)

**3. The interference included Group III subject matter.**

Barton's involved dependent claim 4 also is reproduced below.[3] It will be apparent from claim 4 that the concept of recombining sequences (Group III subject matter) also can be found in the claims involved in the interference and designated as corresponding to the interference count.

**4. The interference included "designing" claims.**

Adang's involved claim 1 and Fischhoff's canceled claim 39 were directed to a method of designing a synthetic *B.t.* gene to be more highly expressed in plants. By including these claims in the interference, the Board considered them to be directed to the same method as well. The Applicants' new claims 113-118 include "designing" steps, and are focused on the "removing problem sequences" invention of the claims currently subject to the restriction requirement.

**5. The interference history indicates that restriction is improper.**

The fact that the method claims that were simultaneously at issue in the earlier interference included the subject matters defining Groups I, II, and III establishes that the Board of Appeals and Interferences would not now deem it necessary or appropriate to restrict the methods of Groups I, II, and III based on their respective starting materials. Adang's and Fischhoff's respective "designing" claims in the interference also establish that new claims 113-118, which do not specify a "starting" sequence, but specify a designing step, should be examined together with the other pending claims. The starting materials simply do not warrant restriction (then or now). The fact that one interference count was previously sufficient to resolve patentability issues for method claims that involve all of the different starting materials

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[3] Barton's claim 4 reads as follows:

> 4. A method as claimed in Claim 1 wherein the chimeric nucleotide coding sequence is synthesized by first synthesizing a coding sequence for a 5' end portion of the coding region for the foreign protein and then joining the synthesized 5' portion to a 3' portion of the native coding region for the foreign protein.

currently at issue demonstrates that the Applicants should be permitted to continue to pursue, together, all of the claims in the current application.

Fairness dictates also such a finding, even if pursuing all of the claims entails payment of additional search fees under the provisions of Rule 1.129. It is prejudicial to use the restriction process during post-interference *ex parte* prosecution to divide the claimed subject matter in a manner that was not envisioned by the parties or the Board during the interference. If additional searching is truly necessary, Rule 1.129 provides a mechanism for compensating the Office for the alleged burden that is imposed.

**B. The starting materials and method steps do not require separate searching.**

The Patent Office's principal basis for restriction is that a search on one method allegedly would not find all art on the other methods because the methods "have different starting materials and different methods steps." The Applicants respectfully disagree.

The premise that all of the groups all have different starting materials is incorrect. For example, claim 67 of Group III specifies one or more *coding sequences* as a starting material. Group I is defined by starting with a coding sequence. Thus, the methods of Groups I and III both recite coding sequence starting materials. They can be searched together, irrespective of whether different starting materials would sometimes necessitate separate searching. (Morover, as discussed in greater detail below, the subject matters of Groups I and III are overlapping.)

Also, focusing on the starting materials, in isolation, does not reflect the nature of the art, or the nature of the search that the Patent Office will perform. The claims that "start with" coding sequences pertain to making a structural gene that encodes an amino acid sequence of an insecticidal protein. The claims that "start with" an amino acid sequence also pertain to making a structural gene that encodes an amino acid sequence of an insecticidal protein. Likewise, the claims that start with more than one portion of a sequence specify combining them to form a structural gene that encodes an insecticidal protein. Plainly, the coding sequence and the amino acid sequence are intertwined in all of the allegedly distinct groups, and it is incorrect to imply that a search for one type of claim would not entail consideration of both coding sequences and encoded amino acid sequences. In fact, the starting steps for claims of all three groups make reference to both coding and amino acid sequences, as exemplified in the

following table, in which coding sequences are underlined and encoded amino acid sequences are bold:

| Starting step of Claim 47 from Group I | Starting step of Claim 59 from Group II | Starting step of Claim 67 from Group III |
|---|---|---|
| (a) starting with a coding sequence, derived from *Bacillus*, that encodes **an insecticidal polypeptide** and that contains a plurality of [problem sequences] . . . . | (a) starting with an **amino acid sequence** of an **insecticidal protein derived from *Bacillus***, wherein wild-type *Bacillus* gene sequence(s) encoding **insecticidal polypeptide(s)** from which the insecticidal protein is derived comprise a plurality of [problem sequences] .... | (a) starting with coding sequences that encode portions of one or more **insecticidal polypeptides derived from *Bacillus***; |

Thus, it is an oversimplification to assert that a claim that recites one type of molecule as a starting material can be searched without consideration of the other type of molecule during the search.

It is true that the method steps involved in making a structural gene differ in wording when starting with an amino acid sequence versus a nucleotide sequence. However, the method steps in all three groups are concerned with making a structural gene with reduced ATTTA sequences and/or polyadenylation signal sequences, compared to, e.g., wildtype *Bacillus* structural gene sequences. All of the groups are related in their stated purpose (method of making a structural gene that encodes an insecticidal protein) and their result (a structural gene that encodes an insecticidal protein, characterized by reduced numbers of the aforementioned problem sequence(s). In fact, the phraseology of "starting with" a particular type of sequence is unnecessary for claiming the invention. New claims 112-118 do not require it, and are generic to all three restriction groups in this respect.

From the foregoing analysis and table, it should be clear that, irrespective of which group is elected (or which "starting material" is involved), the Patent Office will search for art pertaining to making structural genes that encode insecticidal proteins derived from *Bacillus* for expression in plants. Irrespective of the election, the Patent Office will search for art disclosing or suggesting the removal of ATTTA or polyadenylation sequences. Although the

Patent Office asserts that a search on one method would not find all art on the other methods, no evidence for this assertion is offered, and no hypothetical categories of art are identified that would be searched for one group of claims but irrelevant to another group. The analysis of the actual claims shows that this is not the case.[4]

### C. "Separate status and divergent subject matter"

The Restriction requirement includes a boilerplate paragraph to the effect that the inventions "have acquired a separate status in the art because of their recognized divergent subject matter, fields of search, and classification." These assertions are entirely unsupported. What is the separate status? In what way are the subject matters divergent? The foregoing analysis establishes that the Groups are not divergent in subject matter or field of search.

As to classification, the Examiner has classified all three groups within class 435, subclass 89. (Subclasses 91.4 and 91.5 are defined as "indented" under subclass 91.1, and subclass 91.1 is "indented" under subclass 89.) Moreover, the definition of subclass 91.5 (to which Group II was assigned) would appear to describe all three allegedly distinct groups:

> ("Processes wherein the polynucleotide is prepared enzymatically (with no virus, eukaryotic cell, or prokaryotic cell involvement in the preparation step) which results in a new polynucleotide or a polynucleotide different from the starting polynucleotide."[5])

In fact, the definition of subclass 91.5 is more descriptive of the subject matter of the three groups than 91.4 (vector) or 89 (nucleotide).

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[4] Moreover, the Examiner's search burden has been at least substantially addressed by the extensive prior prosecution record and the *inter partes* proceedings in which the present application (or its related applications) have been involved (both before the Board of Appeals and Interferences, in district court litigations, and European proceedings). Materials from these proceedings have been included in Information Disclosure Statements filed by the Applicants. The IDS's, which will be considered irrespective of how many claims are examined, should substantially lessen the Examiner's search burden.

[5] The classification manual further explains, "Viral or cellular involvement, prior to the actual polynucleotide preparation steps, is acceptable for this subclass as is cellular replication of the newly made polynucleotide, if said replication does not modify the structure of the polynucleotide product."

Thus, the inventions are NOT divergent in classification, field of search, or subject matter. For this reason too, the restriction requirement is improper, and should be withdrawn.

**D. No serious burden**

The MPEP instructs that, even if claims are directed to inventions that are deemed patentably distinct, the Patent Office should not issue a restriction requirement if there would be no serious burden examining the claims to the distinct invention. The claims of all three groups specify similar details, including the goal of the method (making a structural gene that encodes an insecticidal protein), the result of the method (a structural gene that comprises a coding sequence that encodes an insectidical protein), and important details about how the result is achieved (starting with sequences derived from *Bacillus*; improving the structural gene by reducing the number of problem sequences (ATTTA or polyadenylation) relative to *Bacillus* sequences (or substantially eliminating them). The searches are substantially identical, and there would be no serious burden examining all of the claims.

**E. Combination-subcombination or genus-species analysis.**

The restriction requirement focuses on the starting materials of the claims of the different groups. For the purposes of restriction or searching, a step that specifies starting with a coding sequence should be thought of as a combination or species, and a step that specifies starting with an amino acid sequence should be thought of in the nature of an essential subcombination, or genus.

The person of ordinary skill who starts with the amino acid sequence is knowledgeable of the genetic code, and therefore can deduce every sequence that encodes the amino acid sequence when the person begins practicing the claimed method. However, the claims of Group II that specify starting with the amino acid sequence are *not constrained with respect to working with any particular coding sequence, as a starting material.* By comparison, the person that starts with a coding sequence derived from *Bacillus* also can deduce every other coding sequence, because the person would know the amino acid sequence that is deducible from the starting coding sequence. However, the claims of Group I that specify making a structural

gene with substitutions relative to the starting coding sequence do explicitly specify starting with a coding sequence. Thus, in the context of restriction, the Group I claims should be thought of as a combination or subgenus of the Group II claims requiring a specific coding sequence, rather than as an independent and distinct invention.

The genus-species or combination-subcombination relationship described in the preceding paragraph is evident in the claim language of the "starting with" steps. For example, the starting step of claim 47 (Group I) explicitly mentions the encoded polypeptide, **and** specifies **use of** a coding sequence derived from *Bacillus*: "(a) starting with a coding sequence, derived from *Bacillus*, that encodes an insecticidal polypeptide and that contains a plurality of [problem sequences] . . . ." Because the starting coding sequence encodes an insecticidal polypeptide, the polypeptide is part of the starting step of claim 47.

The starting step of claim 59 (Group II) also mentions both the amino acid sequence and the *Bacillus* gene sequences, but does not specify that it is necessary to work with the *Bacillus* coding sequences: "(a) starting with an amino acid sequence of an insecticidal protein derived from *Bacillus*, wherein wild-type *Bacillus* gene sequence(s) encoding insecticidal polypeptide(s) from which the insecticidal protein is derived comprise a plurality of [problem sequences] . . . ." Thus, a polypeptide sequence is relevant to the starting steps of both claim groups, but only one of the claim groups also specifies use of a specific coding sequence at the start. This relationship is the same as a combination-subcombination relationship, and the MPEP forbids restriction in this circumstance. (See MPEP 806.05(c).)

**F. Linking claim practice**

Finally, even if the restriction requirement is maintained, it should only be maintained with the caveat that it will be modified or lifted upon the allowance of a *linking claim*. For example, a method of making a structural gene that encodes an insectidical fragment of one *Bacillus* protein, fused to a fragment of another *Bacillus* protein, would fall within at least two groups, Group III plus Group I or II. A claim that covers the making of such a construct is a linking claim. New claims 112-118 are linking claims insofar as they are generic to the Groups, or do not require starting with one particular type of sequence. Upon allowance of one or more linking claims, the restriction requirement should be withdrawn, and claims to all of the groups permitted to issue. See MPEP §809-809.03.

## VI. CONCLUSION

Prompt, favorable consideration of the application is respectfully requested. The Patent Office is authorized to charge any fee deficiencies necessary for entry of this submission, and other fees that may arise in this case (other than the issue fee) to deposit account no. 13-2855, under order number 28079/41785.

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Respectfully submitted,

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